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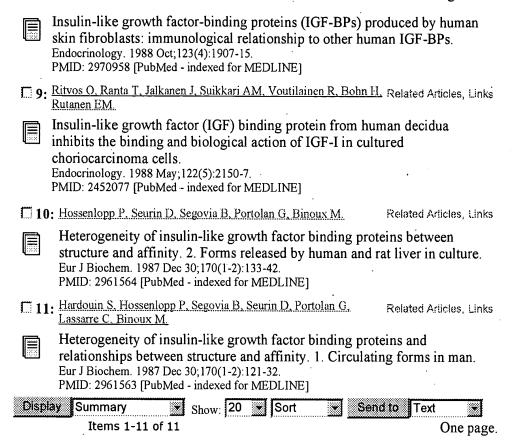


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The BPS domain of Grb10 inhibits the catalytic activity of the insulin and IGF1 receptors.

Stein EG, Gustafson TA, Hubbard SR.

Skirball Institute of Biomolecular Medicine, Department of Pharmacology, New York University School of Medicine, NY, 10016, USA.

Grb7, Grb10 and Grb14 comprise a family of adaptor proteins that interact with numerous receptor tyrosine kinases upon receptor activation. Between the pleckstrin homology (PH) domain and the Src homology 2 (SH2) domain of these proteins is a region of approximately 50 residues known as the BPS (between PH and SH2) domain. Here we show, using purified recombinant proteins, that the BPS domain of Grb10 directly inhibits substrate phosphorylation by the activated tyrosine kinase domains of the insulin receptor and the insulin-like growth factor 1 (IGF1) receptor. Although inhibition by the BPS domain is dependent on tyrosine phosphorylation of the kinase activation loop, peptide competition experiments indicate that the BPS domain does not bind directly to phosphotyrosine. These studies provide a molecular mechanism by which Grb10 functions as a negative regulator of insulin- and/or IGF1-mediated signaling.

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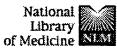
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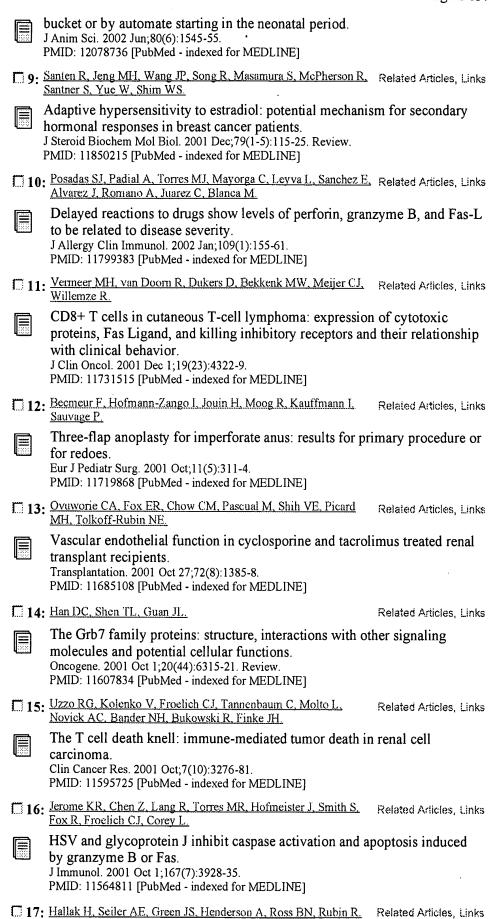
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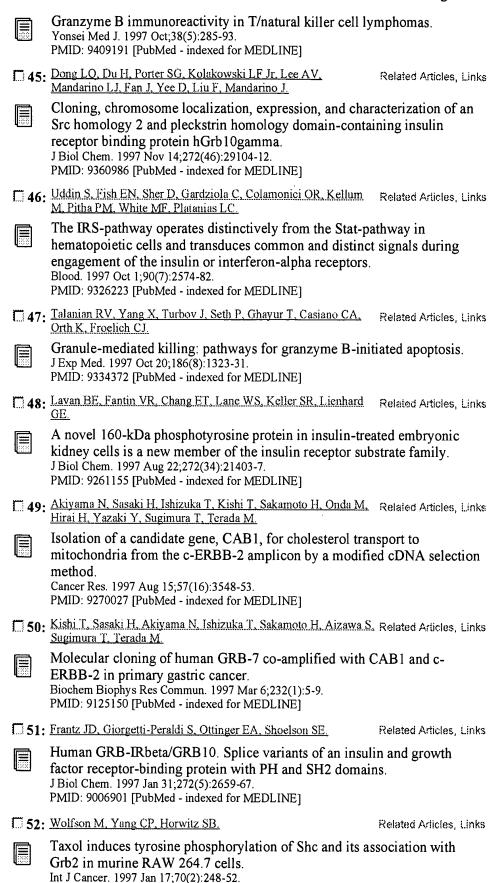
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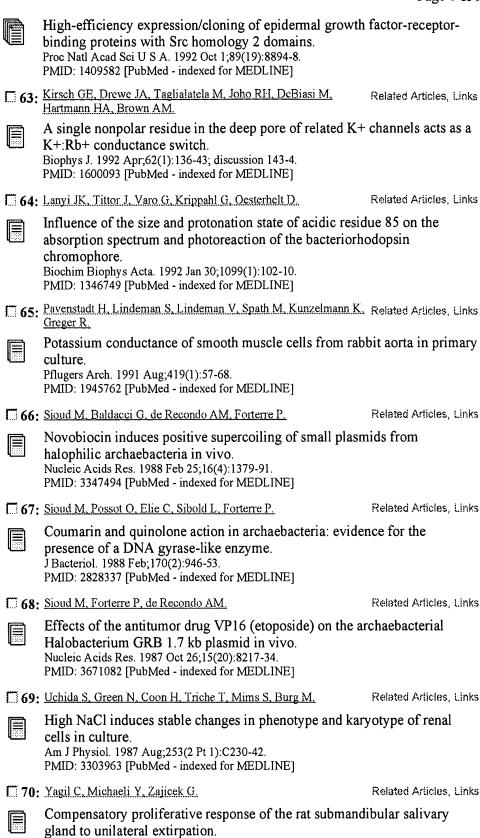
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